Exhibit N

Ultrasound Obstet Gynecol (in press)
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.3962

Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele

R. TUNN, A. PICOT, J. MARSCHKE and A. GAURUDER-BURMESTER

Department of Urogynecology, German Pelvic Floor Center, St. Hedwig Hospitals, Berlin, Germany

KEYWORDS: polypropylene mesh; recurrent prolapse surgery; ultrasound

ABSTRACT

Objective *To investigate whether the sonographically measured size of the mesh implant in women who had undergone vaginal polypropylene mesh repair 6 weeks previously correlates with the original size of the mesh and whether the mesh ensures complete support of the anterior or posterior compartment.*

Methods *Forty postmenopausal women with anterior or posterior vaginal wall prolapse and sonographically proven cystocele (n = 20) or rectocele (n = 20) were evaluated preoperatively and 6 weeks after vaginal mesh repair. Introital ultrasound was performed to identify the polypropylene mesh and measure its distal to proximal length and configuration as well as its thickness. The initial mesh length was compared with that measured by ultrasound 6 weeks postoperatively. Vaginal length was measured pre- and postoperatively.*

Results *The mean ± SD age of the women was 68 ± 7 years. The 20 women with cystocele underwent repair by means of anterior transobturator mesh implantation; the initial mesh length was 6.8 ± 1.1 cm versus 2.9 ± 0.6 cm postoperatively. The 20 women with rectocele underwent repair by posterior transischioanal mesh implantation; the initial mesh length was 9.9 ± 0.8 cm versus 3.3 ± 0.5 cm postoperatively. The mesh supported 43.4% of the length of the anterior vaginal wall and this value was 53.7% for the posterior wall (P = 0.016).*

Conclusion *Sonography is recommended for postoperative evaluation of the anterior and posterior mesh positions after prolapse surgery. There is a considerable discrepancy between the implanted mesh size and the length measured 6 weeks later by postoperative ultrasound. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Transobturator and transischioanal polypropylene mesh interposition are two tissue replacement techniques using vaginal access that have become very popular in prolapse surgery over the last 2 years. The mesh sizes and shapes vary from one manufacturer to the next and can be adjusted individually by the operator. The mesh width ranges from the width of the intact vagina to that of the pelvic outlet (area between the right and left arcus tendineus fasciae pelvis), while the length is even more flexible and should be adjusted individually to the vaginal length in order to achieve support of the entire vagina. Mesh arms are placed along the transobturator or transischioanal access route and supposedly ensure permanent lateral and posterolateral anchorage of the mesh. Depending on the topography of the access route, various techniques are available for positioning of the mesh arms (helical needles, curved needles, plastic sheets and sheaths) to ensure tissue-sparing insertion. Long-term results showing whether the theoretical assumptions underlying mesh interposition actually translate into successful prolapse repair are not yet available. However, the short-term data suggest that the concept is feasible, but also show that 5.3% of women suffer recurrent prolapse as early as 3 months after surgery, despite permanent tissue replacement[1]. Based on earlier experience with ultrasound evaluation of the polypropylene tape in women after tension-free vaginal tape (TVT) repair[2], we conducted the present study to determine sonographically the postoperative size of the mesh implant, to compare it with the size of the implanted mesh, and to evaluate whether full support of the anterior or posterior compartment is achieved.

Correspondence to: Dr R. Tunn, German Pelvic Floor Center, St. Hedwig Hospitals, Große Hamburger Str. 11, D-10115 Berlin, Germany (e-mail: r.tunn@alexius.de)

Accepted: 2 December 2006

METHODS

Forty postmenopausal women with anterior or posterior vaginal wall prolapse that recurred after hysterectomy, and sonographically proven cystocele ($n = 20$) or rectocele ($n = 20$), underwent mesh repair after local estrogen therapy and grading of the prolapse using the POP-Q system (pelvic organ prolapse quantification system[3]). Women with a predominant enterocele were not included in the study, because it is our normal practice to perform abdominal sacropexy in these women. All patients underwent clinical and sonographic follow-up 6 weeks after surgery.

All women were examined by preoperative and postoperative introital transvaginal ultrasound in a semireclining position (with standardized bladder filling of 300 mL) using a Cheetah 2000 (B & K Medical Medizinische, Quickborn, Germany) ultrasound system, equipped with a 5-MHz vaginal sector probe with an emission angle of at least 90°. Postoperatively, polypropylene mesh implants were identified in the midsagittal view and the distal-to-proximal length, as well as its thickness, were measured.

During surgery, cystoceles were repaired using anterior transobturator polypropylene mesh interposition (Perigee®, American Medical Systems, Minnetonka, MN, USA and Prolift Anterior®, Gynecare, Ethicon, Sommerville, NJ, USA), while rectoceles were repaired by means of posteriorer transischioanal polypropylene mesh interposition (Apogee®, American Medical Systems and Prolift Posterior®, Gynecare). The anterior transobturator polypropylene mesh has four arms for anchorage (distal arms for positioning of the mesh caudally at the bladder neck and proximal arms for extending the mesh cranially at the apex of the vagina), while the posterior transischioanal polypropylene mesh has two arms (to extend the mesh to the base of the vagina). The meshes from American Medical Systems have mesh arms (1-cm wide) that are covered by plastic sheets and are placed by means of helical needles, while the arms of the meshes from Gynecare (1-cm wide) are pulled through plastic sheaths placed by curved needles. All meshes are light-weight, consisting of monofilament macroporous material. The original lengths of the meshes are: Perigee, 9.5 cm; Prolift Anterior, 11 cm; Apogee, 13.5 cm; Prolift Posterior, 13 cm.

All women were operated on by the same surgeon (R.T.) so that all operations were performed to the same technical standard. The technique comprised colpotomy from the bladder neck (cystocele) or perineum (rectocele) to the apex of the vagina without resection of vaginal wall tissue and fixation of all meshes with non-permanent sutures (Vicryl) on both sides of the apex of the vagina (muscular layer of the vaginal wall) to avoid early shrinkage of the mesh during wound healing. The posterior meshes were additionally attached on the right and left sides at the level of the proximal deep part of the perineum for the same reason.

Statistical analysis

Data were recorded and graphs were produced using Microsoft Excel 2000 9.0.2812 (Microsoft Corp., Redmond, WA, USA). Statistical analysis was performed with SAS System (Local, WIN_PRO, SAS Institute Inc, Cary, NC, USA). Non-parametric tests (Mann–Whitney *U*-test) was used to identify differences between two variables or changes in a variable (e.g. preoperative vs. postoperative). $P < 0.05$ was considered statistically significant. Correlations between two variables were identified using Pearson's correlation coefficient (r). The probability of the zero hypothesis $r = 0$ (no correlation) was tested using the t-test.

RESULTS

The mean ± SD age of the 40 women was 68 ± 7 (range, 49–80) years. Thirty women had had prior prolapse surgery (cystocele and rectocele repair, $n = 21$; cystocele repair, $n = 3$; rectocele repair, $n = 6$). Of the 20 women who had a cystocele (Aa, Ba, Stage II–IV), 13 underwent repair by a Perigee and seven by a Prolift Anterior procedure. Of the 20 women with a rectocele (Ap, Bp, Stage II–IV) 13 were treated with an Apogee and seven by a Prolift Posterior procedure. None of the study patients had recurrent prolapse at the 6-week follow-up ($n = 40$ had Stage 0 for Aa, Ba, Ap and Bp). At follow-up there were no bladder emptying problems after anterior transobturator mesh repair and no bowel emptying problems after posterior ischioanal mesh repair.

The initial mesh lengths (adjusted intraoperatively by the operator) and the mesh lengths measured

Table 1 Length of mesh at implantation and at postoperative sonographic follow-up

Mesh type	*Mesh length (cm, mean ± SD)*		*Post-op mesh length as % of initial length*	*% of vaginal length supported by mesh*
	*at implantation**	*postoperatively*		
Transobturator (cystocele)	6.8 ± 1.1	2.9 ± 0.6	43.2	43.4
Perigee	6.4 ± 1.2	2.9 ± 0.6	45.4	43.7
Prolift Anterior	7.5 ± 0.4	3.0 ± 0.8	39.3	42.9
Transischioanal (rectocele)	9.9 ± 0.8	3.3 ± 0.5	33.6	53.7
Apogee	10.3 ± 0.7	3.4 ± 0.6	32.8	55.5
Prolift Posterior	9.1 ± 0.4	3.2 ± 0.4	35.2	50.3

*Initial mesh length (adjusted intraoperatively by the operator).

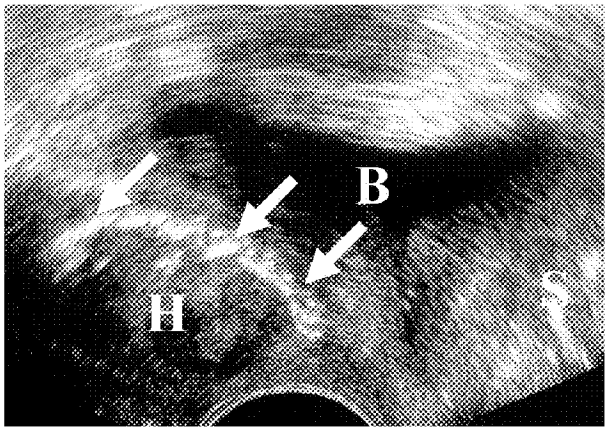

Figure 1 Introital ultrasound image (midsagittal view) showing the hyperechoic polypropylene mesh (arrows) with a flat configuration 6 weeks after transobturator mesh interposition for cystocele repair. The mesh is located under the bladder neck and bladder base within the vesicovaginal space. The convexity of the mesh towards the urinary bladder is caused by a hematoma (H). B, bladder; S, symphysis.

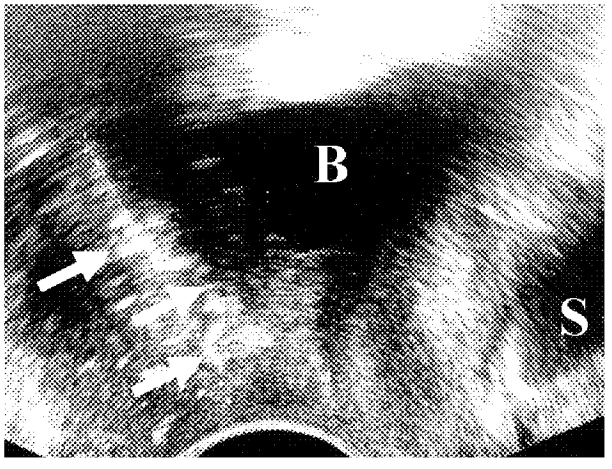

Figure 2 Introital ultrasound image (midsagittal view) showing the hyperechoic polypropylene mesh (arrows) with a wavy configuration 6 weeks after transobturator mesh interposition for cystocele repair. The mesh is located under the bladder neck and bladder base within the vesicovaginal space. B, bladder; S, symphysis.

distally to proximally by ultrasound postoperatively, as well as the length of vagina supported by the mesh, are shown in Table 1. The vaginal length stabilized by transischioanal mesh interposition was significantly greater than was the length stabilized by transobturator mesh interposition ($P = 0.016$); the sonographically measured mesh length relative to the length at surgery was likewise significantly greater for transischioanal than it was for transobturator interposition ($P = 0.0005$). There was no significant difference in these parameters between the two transobturator meshes (Perigee vs. Prolift Anterior, $P = 0.32/P = 0.21$) or between the two transischioanal meshes (Apogee vs. Prolift Posterior; $P = 0.33/P = 0.33$) used in the study. At ultrasound

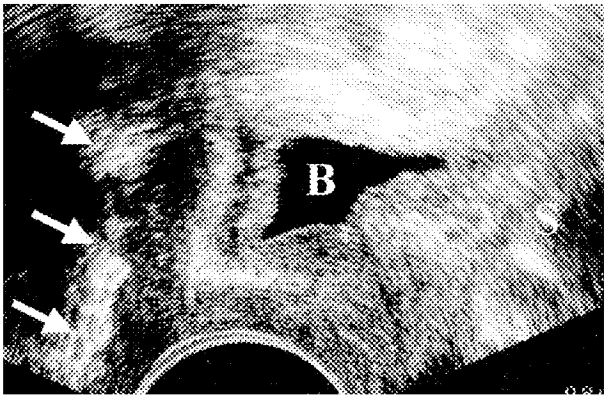

Figure 3 Introital ultrasound image (midsagittal view) showing thickening of the hyperechoic polypropylene mesh (arrows) 6 weeks after transischioanal mesh interposition for rectocele repair. B, bladder; S, symphysis.

follow-up, all 40 meshes showed thickening and a wavy configuration as compared with TVT[2].

The pre- and postoperative vaginal lengths did not differ significantly after either anterior transobturator mesh (8.9 vs. 8.8 cm) or posterior ischioanal mesh (8.4 vs. 8.2 cm) implantation.

One patient developed a hematoma after anterior mesh interposition (Figure 1) but the ultrasound findings (mesh folding) did not differ from those in the other women (Figures 2 and 3).

DISCUSSION

Vaginal mesh repair is very popular, because of the elegance of transobturator or transischioanal access, the ease of application using the manufacturers' needles and the variable mesh sizes that can be further cut to size intraoperatively, the fact that no laparotomy is needed, the option of achieving permanent tissue replacement after failure of fascial reconstruction, and, according to Ulmsten *et al.*[4], the excellent experience with similar materials used for TVT procedures.

The mesh implants employed in this study had a configuration designed to extend from the bladder neck to the vaginal apex (vesicovaginal space) when used for support of the anterior vaginal wall, and from the perineum to the vaginal apex, occupying the rectovaginal space, when used for posterior repair. The available mesh lengths were such that they could be shortened intraoperatively to fit the required anatomical length.

Two findings are noteworthy. The mesh lengths measured sonographically *in vivo* were much shorter than were the implanted mesh lengths, and the lengths did not correspond to the postoperative vaginal lengths. This discrepancy means either that the theoretical concept of mesh interposition is not fully realized or that ultrasound does not visualize completely the proximal parts of the mesh. To exclude incomplete demonstration by ultrasound, we performed not only introital sonography

but also transvaginal sonography to visualize reliably the proximal mesh portions. A definitive answer cannot be given here and further studies are needed. Nevertheless, ultrasound is the preferred modality, especially in comparison with magentic resonance imaging (MRI)[2], as it has been shown to allow good evaluation of polypropylene material.

The proximal mesh arms were positioned about 1 cm distal to the ischial spine anteriorly at the level of the arcus tendineus fasciae pelvis and posteriorly at the level of the coccygeus muscle. In cadaveric studies, this placement has been shown to ensure complete expansion of the mesh[5]. Shortening of the mesh 6 weeks postoperatively may be due to intraoperative or postoperative stresses acting on the mesh, with distal retraction of the proximal mesh arms, or to a change in the configuration of the mesh because the mesh is surrounded by connective tissue. The wavy appearance and thickening of the mesh on sonography supports the possibility that there is concertina-like folding of the mesh *in vivo*. With regard to the most suitable anatomical site for anchorage, Boukerrou *et al.*[6] demonstrated that the sacrospinous ligament provides more stability than does the pelvic floor muscle. Moreover, the arms of a polypropylene mesh should be at least 1 cm wide[6], which was the case for the meshes used in our study. Long-term follow-up results are required to determine how factors such as site of anchorage and width of mesh arms will affect the risk of recurrence. Some effect is likely since recurrence has been reported in 5.3% of patients only 3.6 months after vaginal mesh repair[1], involving predominantly the vaginal vault, although these researchers did not measure mesh lengths by ultrasound and data from other reports in the literature are not available for comparison.

While the vaginal mesh repair techniques used in our study were characterized by standardized mesh placement, it cannot be excluded that different surgical steps may affect the postoperative extension of the mesh. We therefore tried to minimize the impact of such factors by having only one operator perform all interventions. Thus, anterior and posterior colpotomy always extended to the apex of the vagina, no vaginal wall tissue was resected, and the mesh arms were attached to reproducible anatomical sites in the true pelvis (bladder neck, ischial spine). Our study did not investigate whether the mesh length measured by postoperative ultrasound in our patients was affected by the fact that no additional fixation stitches were placed (non-permanent stitches at the level of the apex of the vagina for both meshes and the level of the proximal part of the perineum for the posterior mesh). However, correlation of the total vaginal length and the length of the implanted mesh (minus the length of the urethra (anterior) and the perineum (posterior)) showed that the non-permanent stitches for additional mesh fixation do not influence the mesh position. Future studies must therefore address this issue.

Our results can be discussed in comparison with sonographic findings in patients after TVT repair, because the tapes consist of similar material and the theoretical concept of tension-free stabilization is the same for both approaches. In this case, too, the generally adopted, standardized approach was to aim at midurethral stabilization until studies demonstrated the usefulness of ultrasound for depiction of the polypropylene tapes[2], and it has been shown that not all tapes are actually positioned under the mid-urethra[7] (67.7% midurethral tape position) and that while mid-urethral tape position does not guarantee surgical success[8], a deviant tape position at the level of the proximal urethra may be responsible for postoperative dysfunction[9].

In conclusion, introital and vaginal ultrasound allow excellent depiction of polypropylene meshes. The technique is based on previous experience with the sonographic evaluation of the polypropylene tape after TVT repair. Since vaginal mesh repair is a fairly recent approach that is still under scientific investigation, ultrasound seems to be an indispensable tool for postoperative evaluation. The observed discrepancy between the mesh length at surgery and the sonographically measured length at follow-up urgently requires further evaluation and should be taken into consideration in the further development of new products.

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